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Title Page

Title: The Journey Between Brain and Gut: A systematic review of psychological mechanisms of treatment effect in Irritable Bowel Syndrome.

Sula Windgassen, Rona Moss-Morris, Kimberley Goldsmith, Joseph Chilcot, Alice Sibelli and Trudie Chalder

Authors:

1. Sula Windgassen

Department of Psychological Medicine, Institute of Psychiatry, King's College London, Denmark Hill, London, SE5 8AZ, United Kingdom

Sula.1.windgassen@kcl.ac.uk

2. Professor Rona Moss-Morris

Department of Psychology, Institute of Psychiatry, King's College London, Guy's Hospital, London Bridge, London, SE1 9RT, United Kingdom

Rona.Moss-Morris@kcl.ac.uk

3. Dr Kimberley Goldsmith

Department of Biostatistics, Institute of Psychiatry, King's College London, 16 De Crespigny Park, London, SE5 8AF

Kimberley.goldsmith@kcl.ac.uk

4. Dr Joseph Chilcot

Department of Psychology, Institute of Psychiatry, King's College London, Guy's Hospital, London Bridge, London, SE1 9RT, United Kingdom

Joseph.chilcot@kcl.ac.uk

5. Alice Sibelli

Department of Psychology, Institute of Psychiatry, King's College London, Guy's Hospital, London Bridge, London, SE1 9RT, United Kingdom

Alice.sibelli@kcl.ac.uk

6. Professor Trudie Chalder (corresponding author)

Department of Psychological Medicine, Institute of Psychiatry, King's College London, Denmark Hill, London, SE5 8AZ, United Kingdom; Chronic Fatigue Research & Treatment Unit, Maudsley Hospital, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, SE5 8AZ

Trudie.Chalder@kcl.ac.uk

Tel: +44(0)20 7848 0406

Word Count: 4970

*Requests for reprints should be addressed to Prof Trudie Chalder, Department of Psychological Medicine, Institute of Psychiatry, King's College London, Denmark Hill, London, SE5 8AZ, United Kingdom, Trudie.Chalder@kcl.ac.uk

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Abstract

Purpose: Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain and altered bowel habits. It is estimated to affect 10-22% of the UK population. The use of psychological interventions in IBS is increasingly empirically supported, but little is known about the mechanism of psychological treatment approaches. The present systematic review aimed to investigate the mechanisms of psychological treatment approaches applied to IBS.

Methods: The systematic review included studies conducting mediation analysis in the context of psychological interventions for IBS, focusing on the outcomes of symptom severity and/or quality of life (QoL).

Results: Nine studies in total were included in the review. Eight of the studies assessed mediation in the context of cognitive behavioural-based interventions and one study assessed mediation in a mindfulness based stress reduction intervention. Results indicate that change in illness specific cognitions are a key process by which psychological treatments may have an effect on the outcomes of symptom severity and QoL. Furthermore, results suggest that while gastrointestinal specific anxiety may also be a key mechanism of treatment effect, it would appear that general or state anxiety is not. Although less commonly included in mediation analysis, illness specific behaviours may also have a mediating role.

Conclusions: A mediational model amalgamating the results of studies is proposed to illustrate the findings of the review. The model depicts the process by which psychotherapy, changes illness specific cognitions, behaviours and anxiety to achieve reduction in symptom severity.

Abbreviations

ANS – Autonomic Nervous System

BGA – Brain-Gut-Axis

BSSS – Bowel Symptom Severity Scale

CBT – Cognitive Behavioural Therapy

CNS – Central Nervous System

ENS – Enteric Nervous System

GSA – Gastrointestinal Specific Anxiety

GI – Gastrointestinal

HPA Axis – Hypothalamic-Pituitary Adrenal Axis

HT - Hypnotherapy

IBS- A – Alternating IBS

IBS-C – Constipation predominant IBS

IBS- D – Diarrhoea predominant IBS

IBS-SSS – IBS Symptom Severity Scale

MBSR – Mindfulness Based Stress Reduction

PIT – Psychodynamic Interpersonal Therapy

QA – Quality Assessment

QoL – Quality of Life

RCT – Randomised Control Trial

SEM – Structural Equation Modelling

VSI – Visceral Sensitivity Index

Background

Irritable Bowel Syndrome: Definition, Aetiology and Prevalence

Irritable bowel syndrome (IBS) is a chronic disorder that usually involves periods of remittance in between flare-ups that may vary in severity. The diagnosis of IBS is based on the absence of any other physiological markers that explain the experience of symptoms. For this reason many people with a diagnosis of IBS may have undergone several investigative procedures prior to diagnosis. The prevalence of IBS in the general population is estimated to be 10.5% (Wilson et al., 2004). This varies across ages and gender, with women aged between thirty and thirty nine being twice as likely to experience it than men of the same age range (Dalrymple and Bullock, 2008). IBS is associated with impaired quality of life (QoL) and distress (Athanasakos and Emmanuel, 2013, Wu, 2012) as well as high rates of co-morbidity of anxiety (Fond et al., 2014).

The ROME criteria were developed to classify functional gastrointestinal disorders (FGIDs) that were not otherwise explained by structural or tissue abnormalities. The most recent ROME IV criteria asserts that the prevalent symptom of IBS is abdominal pain, which must be associated with changes in bowel movements or stool consistency (Drossman, 2016). The criteria identify four bowel subtypes: constipation predominant (IBS-C), diarrhoea predominant (IBS-D), alternating bowel pattern (IBS-A) and unclassified (IBS-U). These subtypes are categorised based on the proportion of symptomatic stools that are loose/watery or hard/lumpy.

Brain-Gut Axis

Although the cause of IBS remains unclear, increasing credence is given to the Biopsychosocial aetiological model of IBS (Engel, 1981). This proposes that symptoms occur due to an interaction between biological, psychological and social mechanisms (Mayer et al., 2015, Quinton and Keefer, 2014, Van Oudenhove et al., 2016). A physiological system by which this interaction may occur is referred to as the “brain-gut axis” (BGA) (Jones et al., 2006). The BGA is a bidirectional communication between the enteric nervous system (ENS) located in the walls of the gastrointestinal tract, and the autonomic and central nervous systems (Fichna and Storr, 2012). The mechanism of communication involves the autonomic stress response and the endocrine, neuroimmune and neural pathways (Wu, 2012) utilizing the hypothalamic – pituitary- adrenal axis (HPA Axis). A recent review comprehensively explains how the BGA underpins the psychological, social and physiological interactions to contribute to the experience of symptoms in functional bowel disorders (Van Oudenhove et al., 2016). The BGA is therefore the proposed physiological mechanism by which psychological factors can exert effect on physical outcomes such as symptom severity (Van Tilburg et al., 2013).

Psychological Treatments in IBS

It is well established that psychological factors affect both quality of life (QoL) and symptom severity in IBS (Van Tilburg et al., 2013) and psychological

treatments have been developed over the years to target such factors. Meta-analyses and systematic reviews have established the efficacy of psychological treatments in reducing symptom severity in IBS (Ford et al., 2009, Kennedy et al., 2012, Lackner et al., 2004, Li et al., 2014). The most commonly utilized psychological treatments in IBS are considered below in terms of the underlying theoretical model, mechanisms and empirical support.

Cognitive Behavioural Therapy (CBT)

To date the majority of psychological interventions conducted in IBS are CBT-based, with strong empirical support demonstrating its efficacy in reducing symptom severity and enhancing QoL/impact on life (Ford et al., 2014, Ford et al., 2009, Li et al., 2014). This being said, there is not one agreed CBT protocol for IBS and different studies use different models and treatment techniques (Henrich et al., 2015).

Some protocols may put more emphasis on targeting general or state anxiety, as opposed to gastrointestinal specific anxiety (GSA) (Blanchard et al., 2007, Lackner et al., 2007). Protocols focusing on GSA, tend to more heavily utilise exposure-based techniques (Craske et al., 2011, Hunt et al., 2009, Ljótsson et al., 2010). It has also become common for CBT protocols to include mindfulness (Ljótsson et al., 2010, Wolitzky-Taylor et al., 2012). Other protocols follow a three systems model, specifically focusing on the change of illness related cognitions and behaviours (Kennedy et al., 2005, Kennedy et al., 2006b), as opposed to the targeting of thoughts and behaviours more commonly related to

general anxiety. Although there may be shared mechanisms of change across protocol approaches, the way in which treatment works may differ between studies depending on the model and interventions used.

Hypnotherapy

Hypnotherapy (HT) as applied to IBS is called “gut-directed” or “gut-focused” hypnotherapy. The process involves the use of hypnotic techniques that are designed to relax the automatic reaction to symptoms, and allows individuals more control in their cognitive and physical response to them (Gonsalkorale et al., 2004). Sessions consist of induction of a hypnotic state and hypnotic suggestions to reduce threat perception of symptoms. Evidence suggests that this approach is effective in improving both physical symptoms of IBS and enhancing QoL (Miller et al., 2015, Wilson et al., 2006).

There has been substantial interest in the mechanisms of HT in IBS (Simrén, 2006, Spiller et al., 2007, Tan et al., 2005). One of the key mechanisms consistently implicated in the literature seems to be the role of cognitions. One particular study found that after HT, IBS improvement was associated with a reduction in IBS-related cognitions (Gonsalkorale et al., 2004). The authors suggested that the hypnotherapeutic approach used could be regarded as a form of cognitive restructuring as it involved techniques to increase individuals’ perceived control over symptoms.

Psychodynamic Psychotherapy

Psychodynamic psychotherapy for IBS aims to reduce symptoms through enhancing interpersonal relationships, which are purported to be the underlying source of symptomatic complaints (Guthrie, 2002). This approach is called “Psychodynamic-Interpersonal therapy” (PIT). Sessions are designed to provide individuals with insight into the link between interpersonal difficulties and symptoms, and between emotions and bowel symptoms. A limited number of studies have assessed the efficacy of PIT for IBS with some support for its efficacy in reducing symptom severity (Svedlund et al., 1983, Creed et al., 2003, Guthrie et al., 1991).

There is not an established model by which PIT is proposed to improve IBS symptoms, however Hyphantis et al (2009) hypothesized that PIT would lead to a reduction in IBS symptoms, by reducing psychological distress associated with interpersonal conflict. This paper assessed the mediating effect of psychological distress on interpersonal distress, finding significant mediation. It did not however assess the relationship between treatment, these processes and the outcome of symptom severity.

Establishing mechanisms of psychological treatments for IBS

The primary way to elucidate mechanistic processes in psychological research is by conducting mediation analysis (Baron and Kenny, 1986, MacKinnon., 2008, Windgassen et al., 2015). This allows potential mechanistic variables to be assessed in the context of the proposed pathway between treatment and

outcome (Kazdin, 2007). A simplistic model of mediation is illustrated in figure 1. This demonstrates how a treatment may cause change in an outcome, by first eliciting change in a mediating variable. An early approach to conducting mediation analysis was proposed by Baron & Kenny (Baron and Kenny, 1986), utilising a series of regressions. Mediation is said to occur where I is shown to no longer influence (or have less of an influence on) O when M is controlled for. This approach is sometimes referred to as the “Causal Steps” approach to mediation (MacKinnon et al., 2002, Mackinnon et al., 2007).

Structural Equation Modelling (SEM) is another statistical method to assess mediation. SEM is sometimes referred to as “path analysis” when it is conducted utilising observed variables (MacKinnon., 2008). SEM can also allow the modelling of relationships between variables utilising underlying latent traits and allows models to account for measurement error (Bollen and Pearl, 2013, MacKinnon., 2008). An advantage to the SEM/path analysis approach to mediation is that it can model multiple outcomes/regressions simultaneously, which allows for longitudinal modelling of multiple measures of mediators and outcomes. In practical terms, this means that the impact of numerous mediators identified by a theoretical model have their impact on outcome assessed simultaneously.

Although the number of studies empirically investigating the efficacy of psychological therapies for IBS have increased, little is known about how psychological treatments work (Murphy et al., 2009). Investigating the key processes involved in creating change in outcome, is important to identify

components of therapy that are necessary for achieving desired outcomes. It therefore also provides opportunity for treatment modification and enhancement. The present review aims to systematically assess psychological variables shown to significantly mediate treatment effect on the outcomes of symptom severity and QoL.

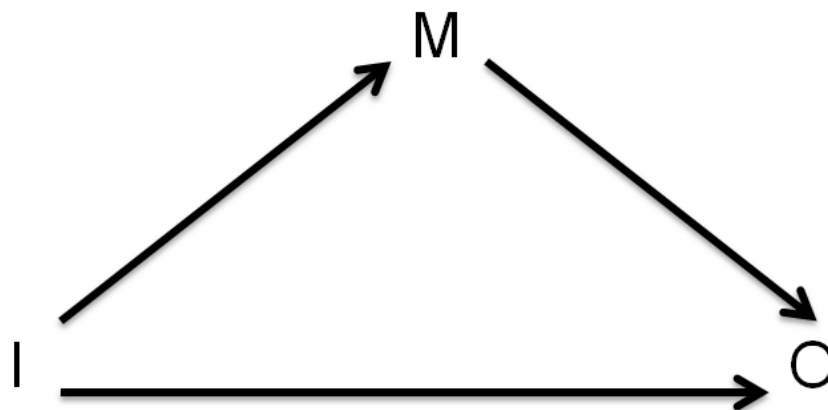


Figure 1: Simplistic Mediation Model: I is the treatment or intervention, M the mediating variable through which I has an effect on O the outcome.

Methodology

The systematic review methods adhered to PRISMA guidelines to ensure the standardised reporting of systematic reviews (Moher et al., 2009).

Literature Search

The search was conducted using electronic databases Ovid, PsycInfo, Embase, MEDLINE, PsycArticles and Global Health. The search was conducted three times in the months April 2014, June 2014, July 2015 and May 2016 (Supplementary Appendix S1). One additional paper was identified by searching citations of the included papers.

Eligible Studies

In accordance with the recommendations of the Centre for Reviews and Dissemination (Chambers et al., 2009), the search strategy was developed using a PICOS format. The acronym refers to (P) population (I) intervention (C) comparator group (O) the outcome or endpoint interested in (S) study design. This shaped the inclusion criteria (Supplementary Appendix S2).

To be included studies had to have conducted mediation analysis on an intervention delivered prospectively. This was to ensure that mediation was designed to test mechanisms of efficacy for delivered interventions rather than to explore potential mechanisms of outcome in the absence of an intervention.

Assessing Study Bias

The Cochrane Handbook stipulates that systematic reviews should assess a risk of bias in included studies (Higgins and Green, 2008). Two separate tools were used. One was designed to assess the overall quality of randomized controlled trials (RCTs) using the original RCT publication and the other was developed to assess the quality of mediation analysis. The RCT quality assessment tool (Supplementary Appendix S3) used was the Cochrane Guide for Quality Assessments (Van Tulder et al., 2003). Only two criteria were not included in the present review. These related to (a) blinding of the participants and (b) blinding of the care provider, which were not practical to use due to the nature of the interventions being studied. Papers were rated as “yes”, “no” or “unclear”

against each criteria. Papers were scored out of a total of 9. Answers of “no” or “unclear” scored 0 and answers “yes” scored 1. This rating is adherent to the recommendations by Cochrane (Higgins and Green, 2008). The papers were rated by the first author and AS.

Two approaches were used to develop the mediation quality assessment tool (Supplementary Appendix S4). Items were based on a previously developed tool (Lubans et al., 2008). Some items were altered to reflect the aims of the present review. Additional items were added to reflect the range in quality across the studies included in review and against standards stipulated in the mediation literature (MacKinnon., 2008).

The additional items were (i) Was more than one model fit criteria reported where path models were used in analysis? (ii) Was the mediator variable/s assessed for change? (iii) Was temporal precedence accounted for in the analysis? (iiii) Did the study report confidence intervals of the mediated effect? When the Baron & Kenny framework was used, it was stipulated that confidence intervals should be used for paths *a* and *b*. Where SEM or path analysis was used, confidence intervals for the indirect path/s were stipulated.

The additional criteria are detailed in order of their listing (i) It is recommended that more than one model fit criteria should be used in SEM because each criteria are affected by different factors (such as sample size, model complexity and data normality) (Hair et al., 1992, McDonald and Ho, 2002) (ii) It was deemed important to establish whether the mediator was assessed for change, to

ascertain whether the interventions were effective in producing change in proposed mediating variables. (iii) Studies were rated on the inclusion of design accommodating temporal precedence as this is an important design consideration to allow inferences regarding causality. (iiii) Confidence intervals were deemed necessary to indicate the magnitude of the path coefficient.

Papers using Baron & Kenny's Causal Steps approach were scored out of 7, whilst other approaches to measuring mediation were scored out of 8. This was because the item regarding assessment of fit criteria was not relevant to the causal steps approach to mediation.

Quality assessment (QA) for mediation was conducted by two of the authors, the first author and the fourth author. The third author was used to rate the quality of one paper to minimize the risk of bias as the fourth author was also an author of this paper. Any disparities were discussed with all raters during quality assessment, enabling full agreement on criteria.

Results

Three hundred and thirty seven search results were returned in the initial search. 317 were excluded after screening titles and abstracts, and removing duplicates (figure 2). The full text of twenty articles were screened and nine were left to review (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Hunt et al., 2009, Jones et al., 2011, Labus et al., 2013, Lackner et al., 2007, Ljótsson et al., 2013, Reme et al., 2011, Wolitzky-Taylor et al., 2012). The most common reasons

for exclusion at the full-text screening phase were studies not performing mediation analysis or not conducting an intervention (Fig 2). Two studies that conducted mediation were excluded as they either did not assess mediation of treatment effect on the outcome of symptom severity or QoL (Hyphantis et al., 2009) or they conducted mediation in the absence of an intervention cross-sectionally (Rutter and Rutter, 2002)

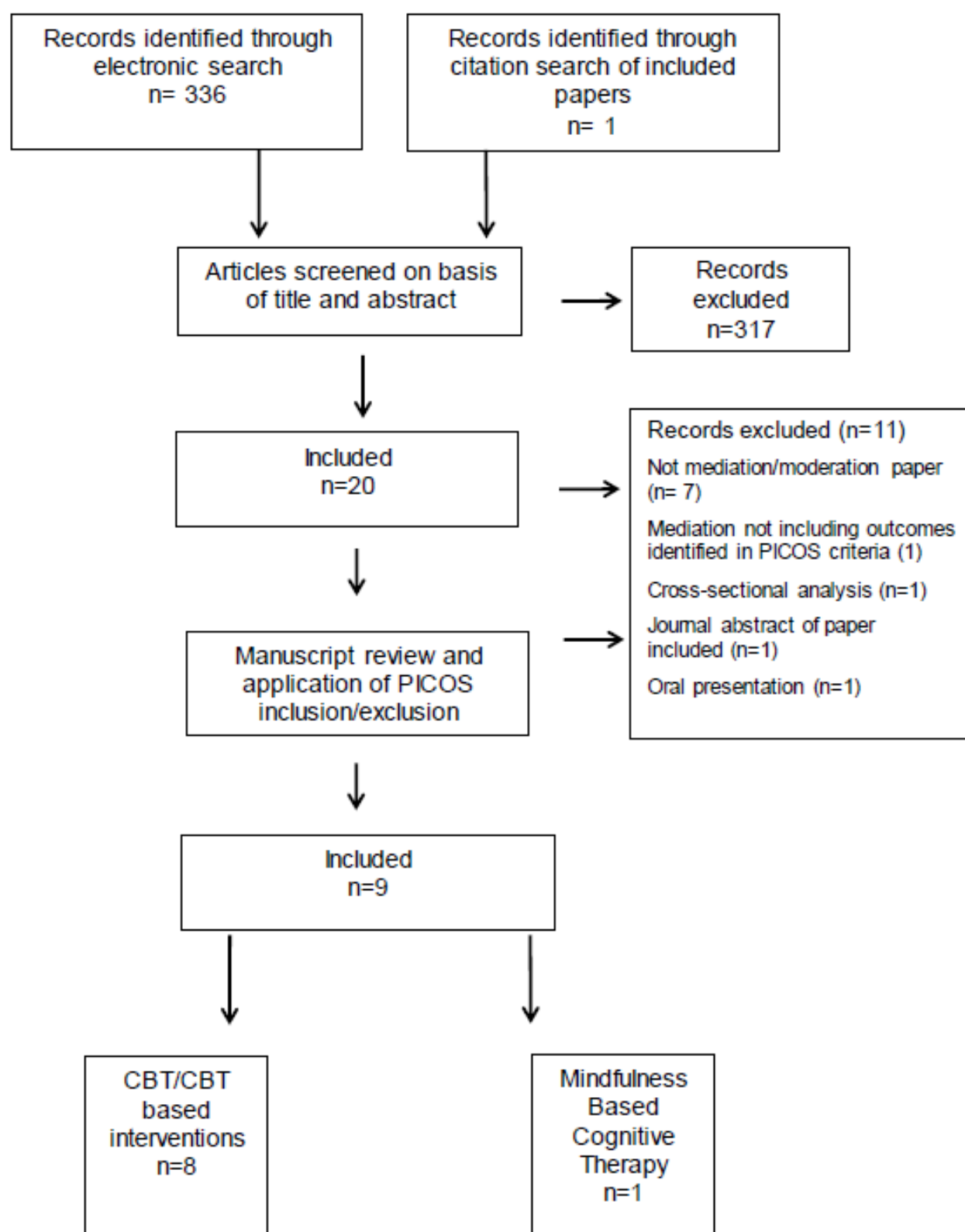


Figure 2: PRISMA Flow Diagram. The figure details how many papers were excluded at each stage of review.

Study Characteristics

All of the studies included were RCTs. Control groups included wait list control (WL) (Hunt et al., 2009, Labus et al., 2013, Lackner et al., 2007), treatment as usual (TAU) (Chilcot and Moss-Morris, 2013, Jones et al., 2011), provision of medication (Reme et al., 2011) and alternative psychological or psycho-education interventions (Garland et al., 2012, Jones et al., 2011, Lackner et al., 2007, Ljótsson et al., 2013, Wolitzky-Taylor et al., 2012). Three studies compared the active treatment with two control groups (Jones et al., 2011, Lackner et al., 2007, Wolitzky-Taylor et al., 2012) and the rest utilised a single control group. Participants were recruited from primary care (Chilcot and Moss-Morris, 2013, Reme et al., 2011), secondary care alone (Labus et al., 2013), a mixture of secondary care and wider community advertising (Garland et al., 2012, Jones et al., 2011, Lackner et al., 2007, Ljótsson et al., 2013, Wolitzky-Taylor et al., 2012) and from online IBS support resources (Hunt et al., 2009). Sample sizes ranged from 54 to 195 (median =76). The follow up periods for assessing outcome measures ranged from three months to 12 months. The range of follow up periods for outcomes included in the mediation analysis was six weeks to eight months, with only one study including outcomes up to 8 months in the mediation analysis (Chilcot and Moss-Morris, 2013). A summary of the study characteristics is presented in table 1.

Quality Assessment

RCT Quality Assessment

Studies ranged in quality from 4/12 (Hunt et al., 2009, Labus et al., 2013) to 9/12 (Chilcot and Moss-Morris, 2013, Garland et al., 2012). The majority of studies were found to be of moderate quality fulfilling 7/12 or above. (Supplementary Appendix S3).

Mediation Quality Assessment

Three studies met 7/8 or 6/7 of the QA items (Chilcot and Moss-Morris, 2013, Ljótsson et al., 2013, Wolitzky-Taylor et al., 2012). The majority of the rest were of moderate quality fulfilling 4 to 5/8 of the criteria (Hunt et al., 2009, Lackner et al., 2007) (Supplementary Appendix S4).

Population Characteristics

The mean age of participants in each study ranged from 33 to 48. A greater proportion of participants were women (72.5 % or greater) as is generally found in IBS populations (Dalrymple and Bullock, 2008). One study chose to recruit only female participants (Garland et al., 2012), with the reasons for this not explained. Classification into types of IBS differed across studies. Only one study used the ROME I (Jones et al., 2011) or III criteria (Ljótsson et al., 2013). The majority of recruited participants conformed to ROME II criteria (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Labus et al., 2013, Lackner et al., 2007, Wolitzky-Taylor et al., 2012). One study relied on GP diagnosis of IBS (Reme et al., 2011) and another on self-reported IBS (Hunt et al., 2009).

The measures of illness severity included the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) (Francis et al., 1997), the Gastrointestinal Symptom Rating Scale modified for IBS (GSRS – IBS) (Wiklund et al., 2009), the Bowel Symptom Severity Scale (BSSS) (Boyce et al., 2000), a composite BSSS measure (Wolitzky-Taylor et al., 2012), a global gastrointestinal rating using a 20 point rating scale (Labus et al., 2013) and a physician rated severity score ranging from symptoms absent to very severe symptoms (Lackner et al., 2007). Samples consisted of participants suffering with moderate to severe symptoms. One study did not use classifications of mild to severe symptom severity, but instead provided means out of a total possible score of 40 for frequency, distress and interference of symptoms (Jones et al., 2011).

Therapy Models & Interventions

Nine of the studies assessed mediation in the context of cognitive behaviourally based interventions. Protocols varied across studies as reflected in table 3. One study conducted mindfulness based stress reduction (MBSR) tailored to IBS symptoms (Garland et al., 2012). The method of intervention delivery, duration of sessions and period of interventions are summarised in Table 1.

Hypothesized Pathways

The hypothesized pathways of change are illustrated in figure 3. It is important for mediation analysis to be conducted according to a hypothesized model rather than as an exploratory exercise (Johansson and Høglend, 2007). Accordingly, it would be expected that studies would assess models of mediation to match the stated hypothesized pathways. One paper presented two contrasting hypothesized pathways (represented by *a* and *c* in Figure 3) (Lackner et al.,

2007). However the final model that was evaluated includes additional paths incorporating QoL. This appears to be exploratory modelling aiming to achieve the second aim of the paper, which was stated as “to examine the interrelationships among symptom improvement, QoL and distress”. Another paper did not state a directional hypothesis regarding which variables were likely to mediate treatment effect but rather hypothesized that numerous variables may do so without a pre-specified mediation model (Labus et al., 2013).

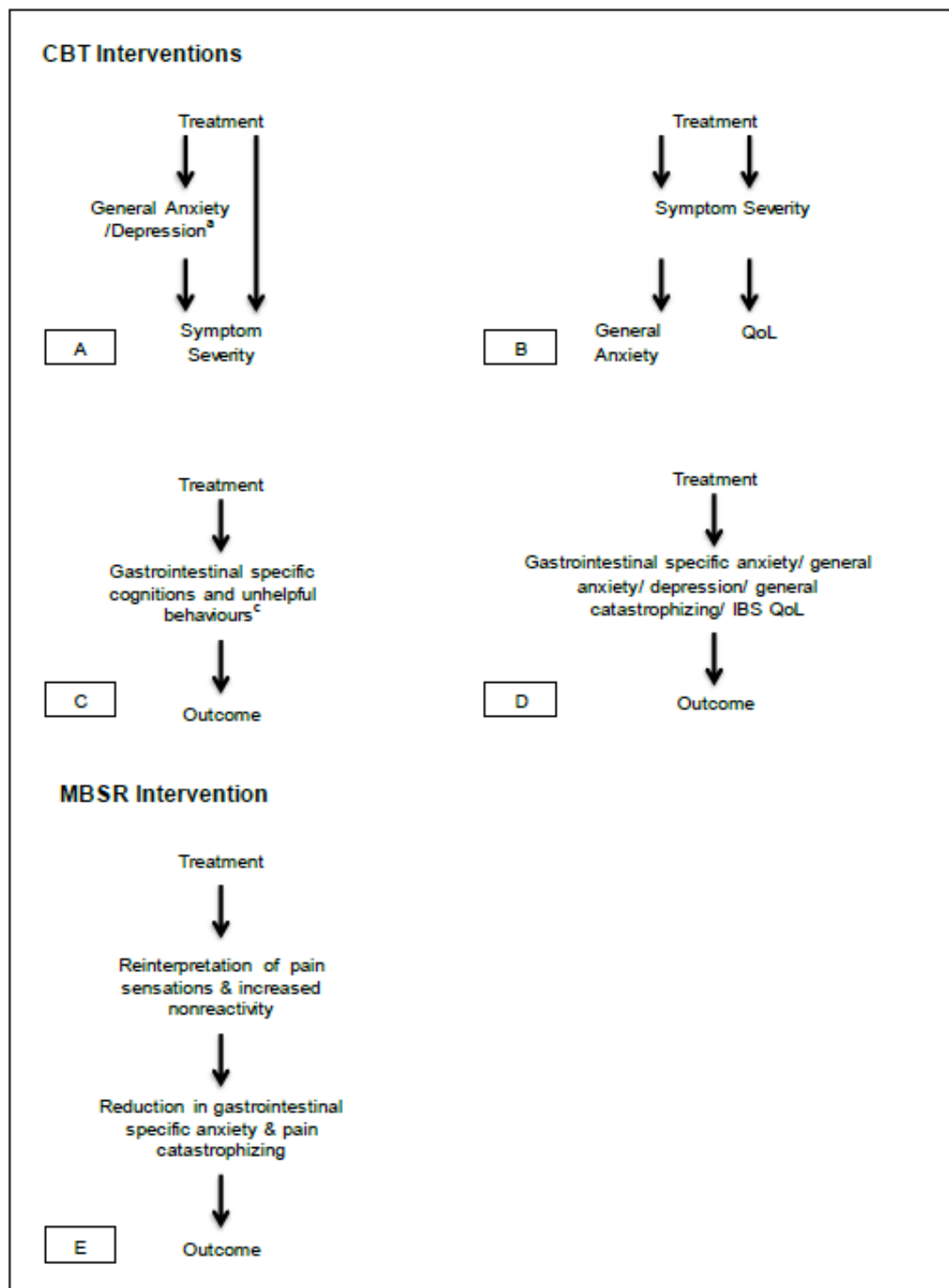


Figure 3: Hypothesized mediated pathways; The diagrams illustrate the hypothesized mediation pathways across papers included in review. The letters indicate which hypothesized pathways were identified in which papers. A. (Jones et al., 2011, Lackner et al., 2007) B. (Lackner et al., 2007) C. (Hunt et al., 2009, Ljótsson et al., 2013, Wolitzky-Taylor et al., 2012) E. (Labus et al., 2013) F. (Garland et al., 2012) ^a= (Jones et al., 2011) ^b= (Hunt et al., 2009) ^c= Reme et al (Reme et al., 2011) included gastrointestinal specific behaviours and Chilcot & Moss-Morris (Chilcot and Moss-Morris, 2013) included general unhelpful behaviours

Mediators

Results of analyses are grouped by the specific mediator variables entered into the models.

Mediators of treatment effect on symptom severity outcome

Perceived Stress

One study assessed perceived stress as a mediator of treatment effect (Labus et al., 2013). This was not a significant mediator.

Cognitions & Metacognitions

Four studies investigated whether both cognitions and general anxiety/psychological distress mediated the treatment effect (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Hunt et al., 2009, Labus et al., 2013). Of these, three found that cognitions rather than anxiety mediated the treatment effect (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Hunt et al., 2009), while one did not (Labus et al., 2013). Of these studies, one study assessed all mediators simultaneously (Garland et al., 2012) and three conducted mediation analyses for each mediator separately (Labus et al., 2013, Chilcot and Moss-Morris, 2013, Hunt et al., 2009).

In addition, one study assessed cognitions as a mediator of treatment effect without a measure of anxiety/psychological distress. This found that cognitions significantly mediated symptom severity along with behaviours (discussed below)(Reme et al., 2011).

The types of cognitions that mediated treatment effects included negative illness-specific beliefs (Chilcot and Moss-Morris, 2013, Reme et al., 2011), pain-specific catastrophizing (Garland et al., 2012) and general catastrophizing (Hunt et al., 2009) (table 2). The illness-specific beliefs measure used by Chilcot & Moss-Morris (Chilcot and Moss-Morris, 2013) was the Brief Illness Perception Questionnaire tailored to IBS. This measured beliefs about the chronicity, seriousness, and controllability of IBS symptoms. The Cognitive Scale for Functional Bowel Disorders (CSFBD), used by Reme et al (Reme et al., 2011) measured the degree of unhelpful beliefs about IBS, with specific items about interpretations of bowel symptoms and reactions to them. Metacognitions were also found to be significant mediators of treatment effect (Garland et al., 2012). These included non-reactivity and reinterpretation of pain.

General Anxiety or Psychological Distress

Of the three studies that investigated the mediating role of anxiety, one found a significant mediated effect in participants who had low baseline QoL (Labus et al., 2013) and one did not find a significant mediated effect of anxiety (Jones et al., 2011). The third did not report confidence intervals, effect sizes or significance levels of the path containing distress as a mediator (Lackner et al., 2007) (Table 2). The extent to which the model fit the data was also not reported in this paper.

Jones et al., (Jones et al., 2011) tested whether both anxiety and depression had a mediating role in a path model that included a feedback loop from anxiety and

depression to symptom severity, and a direct path from treatment to symptom severity. The model was not found to fit the data adequately and individual confidence intervals, effect sizes or significance levels were not reported for individual mediation paths for either variable. Labus et al (Labus et al., 2013) also investigated the mediating role of depression but found no significant mediation.

Gastrointestinal Specific Anxiety (GSA)

Two studies assessed the GSA utilising the Visceral Sensitivity Index (VSI) (Labus et al., 2004) individually as a mediator of treatment effects (Ljótsson et al., 2013, Wolitzky-Taylor et al., 2012) both finding significant mediation. One found that reduction in GSA mediated treatment effect for the intervention group but this did not differentiate from the two comparative control groups (Wolitzky-Taylor et al., 2012).

In the three other studies in which GSA was included as a mediator along with other variables, one found it to be a significant mediator along with other cognitive and metacognitive measures (Garland et al., 2012). One study used an alternative measure to the VSI and did not find significant mediation of GSA (Hunt et al., 2009). It did however conclude that there was marginal mediation with indirect effects yielding a significance of $p=.09$. The third study did not find GSA to be a significant mediator (Labus et al., 2013).

Behaviours

Behavioural responses were assessed as mediators in two CBT-IS studies, one assessing CBT delivered face-to-face (Reme et al., 2011, Chilcot and Moss-Morris,

2013) and one evaluating a self-management CBT intervention with some minimal face-to-face and telephone therapist contact (Chilcot and Moss-Morris, 2013). The former measured behaviours specific to IBS such as checking stools for abnormalities and avoidance of social events due to bowel symptoms (Reme et al., 2010). The latter measured all-or-nothing and resting/avoidance behaviours related generally to illness but not specifically IBS. These were not found to mediate treatment effect, whereas behaviours specific to IBS did significantly mediate. IBS specific behaviour was found to be a significant mediator in a path following this sequence: treatment → behaviours → cognitions → symptom severity. This model was found to fit the data better than a change in cognitions preceding a change in behaviour. It must however be noted, that the analysis lacked temporal precedence limiting the inferences about order of causality of these mediators. The authors stated that mediation was conducted utilising two time points instead of three, as there was no further change at the third time point.

QoL

One study found this to significantly mediate treatment effect for participants with low baseline QoL, but not for those with medium to high baseline QoL (Labus et al., 2013).

Mediators of treatment effect on QoL outcome

Five of the studies (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Hunt et al., 2009, Lackner et al., 2007, Reme et al., 2011) assessed mediation of treatment

effects on QoL outcomes, including impaired functioning as measured by the Work and Social Adjustment Scale (Mundt et al., 2002). Change in IBS specific cognitions appeared to mediate change in outcome, with three of four studies assessing cognitions as a mediator of treatment on QoL finding significant mediation (Chilcot and Moss-Morris, 2013, Garland et al., 2012, Reme et al., 2011) (table 2). One study found no mediation through anxiety or general and IBS-specific catastrophizing cognitions (Hunt et al., 2009) and another found that reduction in symptom severity mediated improvement in QoL (Lackner et al., 2007). The latter model found significant paths from CBT → symptom severity → QoL → distress → QoL.

Discussion

Summary of results

The review assessed which psychological variables significantly mediated treatment effects on the outcome of symptom severity and/QoL. Eight studies assessed mediation in the context of CBT interventions. The results indicate that both GI specific cognitive change and GSA are key mechanisms by which psychological treatments have effect on both symptom severity and QoL. Four out of five studies assessing cognitions as a mediator found them to mediate the effects of treatment on symptom severity. Three out of five studies assessing GSA as a mediator found significant mediation, and one found a trend towards significant mediation. Of the three studies that assessed general anxiety/psychological distress, only one found it to significantly mediate treatment effect (Labus et al., 2013). This study found evidence of moderated

mediation, in that anxiety was only found to significantly mediate treatment in participants who had low baseline QoL. The stratification of analysis by QoL does unfortunately reduce the power to detect significant mediators and makes results hard to interpret.

Only two studies assessed behavioural responses as a mediator (Reme et al., 2011, Chilcot and Moss-Morris, 2013); one measuring IBS specific behaviours, found it to be a significant mediator (Reme et al., 2011) and the other, measuring more general all-or-nothing (boom or bust) and avoidance behaviour, did not (Chilcot and Moss-Morris, 2013).

Similarly, the trend for mediation of treatment effects on QoL found that changes in cognitions resulted in improved QoL (Reme et al., 2011, Chilcot and Moss-Morris, 2013). Two studies assessed the mediating effect of psychological distress and cognitive factors on QoL. Of these one found no mediation (Hunt et al., 2009) and the other found that a decrease in GSA and pain catastrophizing resulted in an enhanced QoL (Garland et al., 2012). Lackner et al (2007) found a series of significant paths demonstrating that CBT had direct effects on symptom severity and that this influenced QoL (table 2). However, the fit of this path model to the data was not reported and therefore the results should be interpreted with caution.

Quality of Studies

Most studies were classified as moderate to high quality in the RCT QA. The two criteria that were most commonly not met were whether the outcome assessor was blinded and whether compliance was described and acceptable. Often it was unclear as to whether the outcome assessor was blind or not, or what the process for collecting outcomes was. In terms of the compliance of participants to the interventions, this was often not described and where it was, it was low. In one study around 40% of participants were considered not to have completed a full course of therapy (Kennedy et al., 2005, Reme et al., 2011).

Quality as assessed specifically for the mediation analyses was also generally moderate across the studies. All studies included a control group in the analysis and all studies were designed to influence mediating variables as determined by the inclusion criteria. Around half of the studies failed to account for temporal ordering of mediator change prior to outcome change in the analysis by using variables measured at the same time point (Jones et al., 2011, Garland et al., 2012, Hunt et al., 2009, Lackner et al., 2007, Reme et al., 2011). This means that the extent to which causal interpretations can be made is limited. Four studies out of seven that used path analysis or SEM did not make clear whether they used more than one assessment of model fit (Chilcot and Moss-Morris, 2013, Jones et al., 2011, Labus et al., 2013, Lackner et al., 2007). Not reporting a range of model fit indices, reduces transparency as to whether the model fits the data taking into account different factors such as sample size and model complexity.

Five out of the nine studies did not present confidence intervals for the indirect paths (Garland et al., 2012, Hunt et al., 2009, Jones et al., 2011, Lackner et al.,

2007, Wolitzky-Taylor et al., 2012). Neglecting to report confidence intervals in any study employing statistical methods renders it uninterpretable; in these cases it prevents us from gaining insight into the likely values of the mediated effect. Furthermore, a subset of these studies conducted path analysis but did not report path coefficients for the indirect effect (Jones et al., 2011, Lackner et al., 2007). Consequently interpretations of the size or extent of the mediated effect cannot be made without doing further calculations.

Issues with Analysis Comparisons

A predominant limitation of the use of the Baron & Kenny framework utilizing a series of regressions, is that it has low statistical power as compared to SEM or path analysis (Hayes, 2009, MacKinnon et al., 2002, MacKinnon., 2008, Windgassen et al., 2015). It also does not allow for investigation of more complex mediation modeling investigating whether one mediator precedes another or works simultaneously. Different approaches to mediation analysis make study comparison challenging, as some analyses provide more comprehensive assessment of mediation than others.

Another issue complicating the comparison of mediation studies is the inclusion or non-inclusion of covariates. Some analyses control for covariates such as baseline measures of the outcome, mediator variable or both. Inclusion of covariates is recommended in order to reduce bias in mediation effect estimates, and leads to a greater understanding of the influence of potential confounding variables (MacKinnon and Pirlott, 2015, Mackinnon et al., 2007, VanderWeele,

2015). Less than half of the papers included in the review included covariates in the analysis. It is generally straightforward to adjust for baseline measures of mediators and outcome, which may be amongst the most important confounders of the mediator/outcome relationship.

The Role of Theory

The design of intervention RCTs should be informed by theory, which should include the important mediating variables that are hypothesised to change with treatment and in turn have an effect on outcome/s. It is interesting to note that four out of nine papers assessed the mediating role of anxiety/psychological distress, without an inclusion of a cognitive measure. This is despite the fact that the majority of studies referenced a cognitive behavioural model as a basis for informing intervention design.

Gastrointestinal Specific Anxiety Versus General Anxiety

All studies except one (Hunt et al., 2009) measuring GSA utilised the VSI (Labus et al., 2004). The VSI incorporates items that pertain to feelings of anxiety specifically relating to IBS symptoms, as well as IBS specific cognitions and behaviours. The other measure of GSA was not a validated measure. The authors used items from a general anxiety scale that had been tailored to apply to specific IBS related symptoms (Hazlett-Stevens et al., 2003). There may be an argument for the development of a scale that specifically measures GSA, without the inclusion of cognitive and behavioural items. Such a measure may allow the

elucidation of the relationship between illness specific cognitions, behaviours and GSA.

The review suggests that psychological treatments achieve improved outcomes, predominantly by reducing GSA, rather than general anxiety. Analysis conducted by Garland et al (Garland et al., 2012) compared a series of path models to assess how well they fit the data. The model including a general measure of psychological distress was found not to fit the data as well as the final model, which included GSA amongst other variables described earlier. It must however, be acknowledged that there is a high co-morbidity of anxiety in IBS populations (Fond et al., 2014). Consequently, it is likely that psychological approaches targeting general anxiety, may also achieve a reduction in symptom severity. The distinction, between general and GSA is important particularly for treatments provided to individuals with IBS who don't have high general anxiety.

An Assimilated Model of Mediation

A model of mediation for psychological treatment effect is proposed based on the findings of the review (figure 4). The review finds that both illness specific cognitions and GSA are predominant mediators of treatment effect. There is also preliminary evidence that illness specific behaviours have a mediating effect. The paper assessing the role of illness specific behaviours found that change in behaviours preceded change in illness specific cognitions (Reme et al., 2011). This may indicate that interventions targeting IBS specific behaviour change, are effective because this subsequently results in cognitive change. It must, however

be acknowledged, that the study lacked temporal precedence (Reme et al., 2011). This limits the extent to which the sequence of causality can be inferred.

The review opens questions regarding the relationship between illness specific cognitions, behaviours and GSA. It seems likely that there is a bidirectional relationship between symptoms of GSA, cognitions and behaviour. We propose that the relationship between these three variables impact on symptom severity via the autonomic nervous system and HPA axis. These are systems involved in the physiological stress response and key components of the BGA (figure 4) (Kennedy et al., 2014, Kennedy et al., 2012). This makes intuitive sense as the GSA is likely to be predictive of and predicted by autonomic arousal (Mayer and Tillisch, 2011).

This review does not support the hypothesis that psychological treatments are effective in reducing symptom severity by targeting co-morbid anxiety. The implications for psychological treatments delivered for IBS, would be that target for change should be illness specific factors (GSA, cognitions, behaviours) rather than general levels of anxiety.

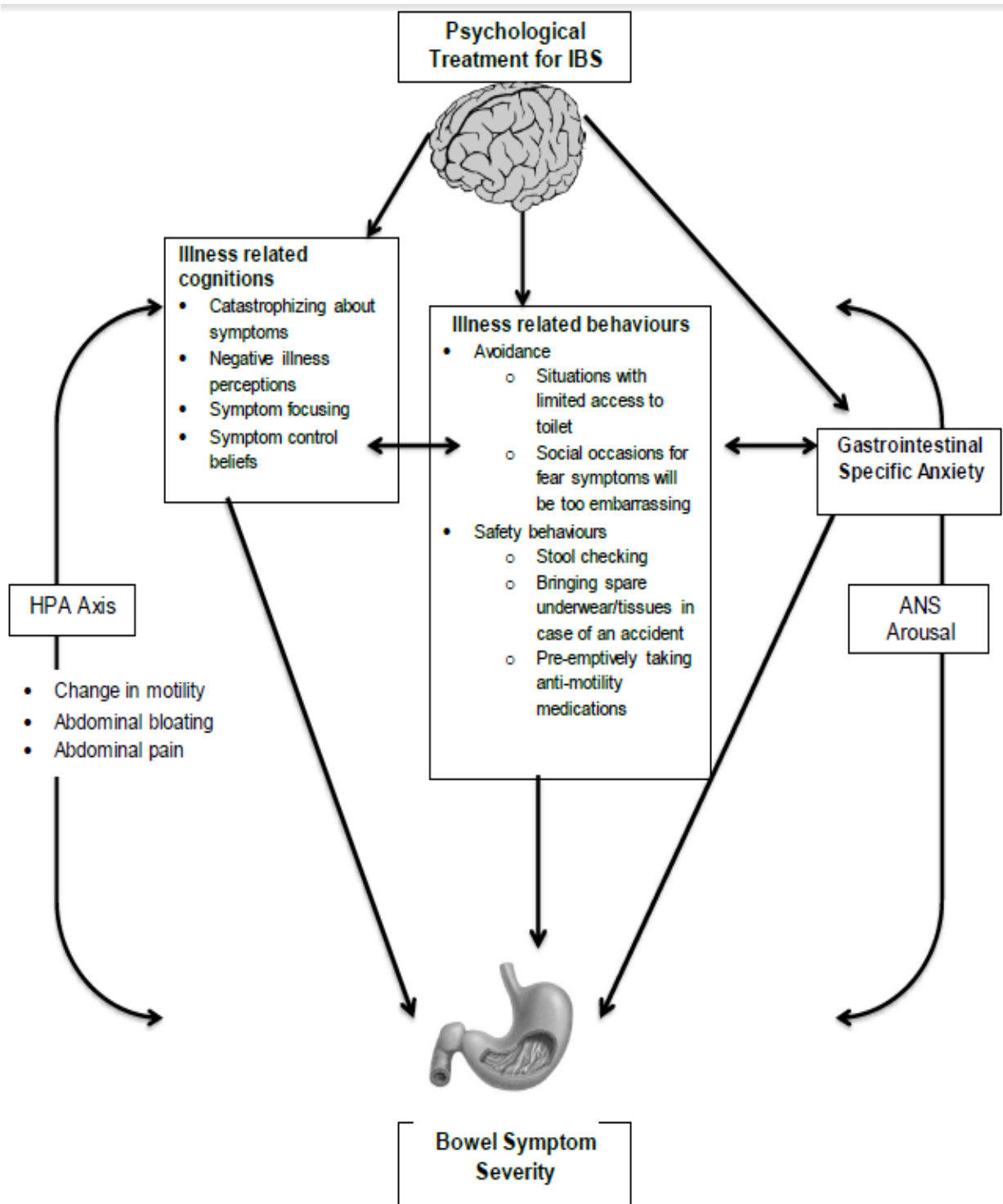


Figure 4: Mediation model of IBS. The figure depicts a hypothesized model of mediation based on the results of the review .

Less Commonly Measured Mediators

Interestingly two studies investigated the potential mediating role of QoL on treatment outcome (Labus et al., 2013, Lackner et al., 2007). One assessed whether the impact of treatment on QoL produced a reduction in symptom severity and the other assessed whether QoL had a mediating role in a path leading from treatment → symptom severity → QoL → distress, including a feedback loop to QoL. The hypothesized mediating role between the studies was therefore rather different. In neither study was a rationale for the investigation of QoL as a mediator presented, although both studies found significant mediation. Intuitively QoL is generally regarded as an outcome measure rather than a mediator measure.

Variables that were not found to mediate the effect of treatment on symptom severity were depression (Jones et al., 2011) and perceived stress (Ljótsson et al., 2013). Such results provide a greater understanding of how to focus treatment, suggesting that depression and stress do not necessarily need to be targeted in order to achieve improve outcomes. Further studies assessing these variables as mediators would be required before definitively drawing this conclusion.

Limitations

The review is limited by the small number of meditational studies that have been conducted to date. Perhaps also due to the empirically based nature of CBT, the majority of the psychological interventions included in review were CBT or designed in accordance with a CBT model. The review was therefore not able to explore mechanisms that may be responsible for change in different therapeutic approaches. Furthermore, potential similarities between different treatment approaches cannot be considered.

Another limitation of the literature reviewed was that the degree of mediation effect could not be uniformly compared across studies. Some papers did not report effect sizes for the mediator variables or paths at all, whilst others presented effect sizes for mediating paths rather than individual variables. The review examines objectively whether mediation was found by considering the significance, confidence intervals and effect sizes available of the indirect effects and path models tested. It does not examine the nuances of individual analyses contained in the discussion of included papers.

Recommendations for Future Mediation Studies

The review highlights the importance of theoretically informed design of mediation studies. Future studies conducting mediation in the context of a psychological intervention should carefully consider what the targets of change are as informed by the prescribed model of treatment. Measurements of these targets for change in the form of validated and reliable questionnaires should be included in mediation models. This would allow more complete mediation

analysis that can accurately assess how well such models fit the data. In the context of mediation studies within psychological treatments for IBS, this would mean that researchers include measurements of anxiety/distress, cognitions and behaviours.

Based on the results of this review, it would appear important for researchers to further elucidate the relationship between cognitive change and change in anxiety, or more specifically, gastrointestinal anxiety. It may be useful to understand whether change in one is dependent on change in the other, or whether change is co-occurring. In addition, few researchers have investigated the potential mediating role of illness-related behaviours. Future studies assessing mediation in this area, should include a behavioural measure to further understand whether this is an important mechanism for change.

Conclusion

There is a clear indication that cognitive change is important for reducing symptom severity as well as enhancing quality of life in IBS. From the minimal investigation into the mechanistic role of behaviour, it seems that the reduction of certain toileting and avoidance behaviour may also be important for improving these outcomes in IBS. Different studies utilized different measures of distress/anxiety with equivocal findings regarding their mechanistic role in psychosocial interventions on outcome. This was further complicated by the use of the VSI, which appears to be a compound measure.

Future mediation studies and models need to include all mediating variables implicated by the theoretical model of treatment. The limited number of studies

to date suggests that it is premature to draw conclusions about the need for the modification of treatment practices. However, the review does provide substantial support for the targeting of unhelpful cognitions as a mechanistic process involved in improving outcomes in IBS.

Conflicts of Interest

Authors 2,4 and 6 authored studies being reviewed in the present review.

Authors 1,2, 3, 5 and 6 are working on a randomised controlled trial assessing the clinical and cost effectiveness of cognitive behavioural therapy in refractory IBS, funded by the Health Technology Assessment Programme.

Table 1: Study characteristics

Study	Study Design	Sample Size	Sample (age, gender, diagnostic criteria)	Control Group	Theoretical Model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Garland et al 2008	RCT	75	100% female Mean age 42 ROME II criteria Receiving TAU	Support group with psycho-education	MBSR	8 weekly 2-hour group sessions and 1 half day retreat. MBSR programme with adaptation for IBS in terms of focal points of meditation & homework including psycho-education on IBS	Certified health coach with 10 years' experience in teaching MBSR in clinical settings	NR	Baseline* Two weeks post treatment* 3 months
Reme et al 2011	RCT	149	82% female Mean age 33 GP diagnosed IBS	Mebeverine alone	CBT	6 weekly 50-min sessions face-to-face. CBT based on Lang's three systems model and adapted to IBS in terms of cognitions and behaviours focused upon. 270mg Mebeverine taken 3 times daily in addition	Four general practice nurses trained to deliver CBT	59% received intervention	Baseline * First follow up at 1.5 months* 3 months 6 months 12 months

Receiving
Mebeverin
e

Labus et al (2012)	RCT	69	72.5% female Mean age 46 ROME II	WL Control	CBT	5 weekly 2-hour group sessions. Intervention consisted of (1) education on neurobiology of stress and IBS in the context of the three systems CBT model (2) psychological focus of role of cognitions and behaviours (3) relaxation training (4) homework including symptom diaries and relaxation training	Lead by a gastroenterologist (45% of sessions) and a therapist (55% of sessions).	NR	Baseline* Post treatment (5 weeks)* 3 months*
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TAU= Treatment as usual, NR= Not reported, * = time point assessment included in mediation analysis

Table 1 Continued: Study characteristics

Study	Study Design	Sample Size	Sample (age, gender, diagnostic criteria)	Control Group	Theoretical Model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Chilcot & Moss-Morris (2013)	RCT	64	73% female Mean age 39 ROME I modified or ROME II receiving TAU	TAU receiving an IBS fact sheet on how IBS diagnosed	CBT	1 one-hour face to face session with a health psychologist and a comprehensive CBT based self-management manual divided into 7 chapters to be completed over 7-8 week period in addition to IBS fact sheet.	Self-management intervention with 1 session with health psychologist	93.5% received intervention	Baseline* Post treatment (2 months)* 5 months 8 months*
Jones et al (2011)	RCT	105	81% female Mean age 42 ROME I	(1) Relaxation therapy. (2) TAU	CBT	8 weekly 1-hour face-to-face CBT sessions. Intervention consisted of a manual-based programme incorporating realistic symptom appraisal, enhanced coping strategies, cognitive restructuring and problem solving. PTs also received TAU and relaxation training.	Clinical psychologist	NR	Baseline* Midpoint (4 weeks)* Post treatment (8 weeks)*

								6 months	1 year.
Hunt et al (2009)	RCT	54	81.5% female Mean age 38 Self report of medical IBS diagnosis	WL control	CBT	5 weekly web delivered modules with homework assignments submitted by email. Individualised feedback given within 48 hours. Modules included (1) psycho- education on biological link between stress and GI symptoms & relaxation training (2) cognitive stress management (3) catastrophic thinking (4) graduated exposure (5) behavioural experiments	Self- management intervention	62% received active treatment and completed 6 week assessment	Baseline* Post treatment (6 weeks)* 3 months (for intervention group only)* t

TAU= Treatment as usual, NR= Not reported, * = time point assessment included in mediation analysis

Table 1 Continued: Study characteristics

Study	Study Design	Sample Size	Sample (age, gender, diagnostic criteria)	Control Group	Model	Intervention (duration, amount, time period)	Intervention delivery (by nurse, therapist)	Adherence to intervention	Time points of assessment in mediation analysis
Lackner et al (2007)	RCT	147	147 PTs 82% female Mean age 48 Rome II diagnosis	Psycho-educational support. WL Control	CBT	10 weekly 90-minute group CBT sessions. Intervention consisted of a manual-based programme incorporating contextual/situational factors associated with flare-ups, unhelpful cognitions, enhancing coping strategies and problem solving abilities.	Three clinical psychologists with average of 10 years experience delivering psychological treatments to painful medical disorders.	90.8% complete d active treatment	Baseline * Post treatment (12 weeks)*
Ljotsson et al (2013)	RCT	195	79% female Mean age 38 ROME III	Internet-delivered stress management	CBT	10-week internet-delivered CBT. Intervention consisted of exposure & mindfulness exercises including (1) exposure to symptoms by engaging in behaviours believed to trigger symptoms (2) reduction of safety behaviours (3) exposure to behaviours normally avoided	Therapist/clinic al psychologist/ psychology graduate student	NR	Weekly from week 1 – 10*

			diagnosis			when experiencing symptoms (4) altering of toileting habits (5) a range of mindfulness exercises to practice daily. Participants also received regular online support.			
Wolitzky et al (2012)	RCT	76	74% female Mean age 39 ROME II diagnosis	Attentional Control or stress management	CBT	10 weekly 50-minute sessions. CBT –interoceptive exposure intervention based on CBT for panic disorder and adapted for the IBS population. Intervention consisted of (1) psycho-education of brain-gut physiological relationship (2) attentional control skills (3) cognitive reframing of specific illness cognitions (4) interoceptive exposure to IBS relevant visceral sensations (5) exposure to behaviours normally avoided when experiencing symptoms	NR	NR	Baseline* Mid-treatment (week 5)* Post treatment (week 10)* Follow up (5 months)
TAU= Treatment as usual, NR= Not reported, * = time point assessment included in mediation analysis									

Table 2: Results

Study	Outcome Variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Garland et al 2008	<ul style="list-style-type: none"> IBS Symptom Severity (IBS-SSS) IBS-Related Quality of Life (IBS-QoL) 	RM-ANOVA	Nonreactivity (FFMQ subscale) Pain Catastrophizing (CSQ pain catastrophizing subscale) Visceral Sensitivity (VSI) Reinterpretation of Pain Sensations (CSQ reinterpreting pain	Significant improvement in non-reactivity, pain catastrophizing, VSI, cognitive reinterpretation of pain and psychological distress.	Path Analysis	5 models mediation models (one full and four partial)	Significant model of full mediation: T→ decreased visceral sensitivity and pain catastrophizing → increased QoL T→ increased reinterpretation of pain and nonreactivity → decreased pain catastrophizing and visceral sensitivity → (and increased reinterpretation of pain → reduced SS.	T→ decreased visceral sensitivity and pain catastrophizing → increased QoL

subscale)

Psychological

Distress (BSI)

Reme	• IBS	Regression	Behaviour	Significant	Path	Compared 2 path models	Partial mediation	Partial mediation
et al	Symptom		Responses	improvement	Analysis	of mediation for full and	T→ behaviour → cognition → SS	T→behaviour → cognition
2011	Severity		Questionnaire	in behavioural		partial mediation: (1) T	with direct path from behaviour	→ WSAS with direct path
	(IBS-SSS)		(BRQ)	scores in CBT		→ behaviour →	→SS	from behaviour →WSAS
			Cognitive Scale	group		cognitions → outcome		
	• Work and		for Functional	Significant				
	Social		Bowel Disorders	improvement		(2) T → cognitions →		
	Adjustment		(FBD)	in cognitive		behaviour → outcome		
	Scale			scores in CBT		for each outcome.		
	(WSAS)			group – but				
				not after 3				
	• Anxiety			month follow				
	(HADS)			up				

ASI= Anxiety Sensitivity Index (Peterson and Heilbronner, 1987) B-IPQ = Brief Illness Perception Questionnaire (Broadbent et al., 2006) BRQ = Behavioural Responses Questionnaires (Reme et al., 2010) BSSS = Bowel Symptom Severity Scale (Boyce et al., 2000) CBSQ = Cognitive and Behavioural Responses to Symptoms Questionnaire (Moss-Morris and Skerrett, 2006) CSQ = Coping Strategies Questionnaire (Rosenstiel and Keefe, 1983) FBD = Cognitive Scale for Functional Bowel Disorders (Toner et al., 1998) FFMQ = Five Facet Mindfulness Questionnaire (Baer et al., 2006) GSRS-IBS = Gastrointestinal Symptom Rating Scale (Svedlund et al., 1988) Global GI SS = Global Gastrointestinal symptom severity, an analogue scale from 0-20 (Labus et al., 2013) GSIBSI = Global Severity Index of Brief Symptom Inventory (Derogatis and

Spencer, 1993) HADS = Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) IBS-QoLa = IBS Quality of Life (Patrick et al., 1997) IBS-QoL b = IBS related Quality of Life (Drossman et al., 2000) IBS-SS = IBS Symptom Severity Score (Francis et al., 1997) WSAS = Work and Social Adjustment Scale (Mundt et al., 2002) VSI = Visceral Sensitivity Index (Labus et al., 2004) VAS= Visceral Anxiety Sensitivity, 5 items developed to assess gastrointestinal specific anxiety (Hazlett-Stevens et al., 2003)

Table 2: Results Tables Continued

Study	Outcome Variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Labus et al (2012)	Symptom Severity (Global GI symptom severity)	Repeated measures GLM	IBS-QoL depression (HADs) anxiety (HADs) Visceral Sensitivity (VSI) Catastrophizing (subscale of CSQ)	Significant positive change at 5 week, and 3 month follow up of: • IBS-QoL • depression • catastrophizing Significant reduction of VSI at 5 weeks	Path Analysis	Moderated mediation model: Baseline QoL = moderator entered into mediation model with IBS- QoL, HADs, VSI, Catastrophizing entered as M variables and GI Severity as outcome	T → IBS-QoL → SS when baseline IBS-QoL was low. T → Anxiety → SS when baseline IBS-QoL was low.	N/A
Chilcot & Moss- Morris (2013)	• IBS-SS • WSAS • HADS	ANCOVA	Brief Illness Perception Questionnaire (B- IPQ) Cognitive and	Significant decrease in catastrophizing, damaging beliefs, and fear avoidance	Path Analysis	Separate path models conducted for each significant mediator to explore the relationship of	Partial mediation T → Illness Perception → IBS-SSS with direct effect of T→SS	Partial mediation T → Illness Perceptions→WSAS with direct effect of T→WSAS

Behavioural	subscales	T → M → Outcome	
Responses to	(cognitions) of the	(for each outcome)	T → Damaging beliefs →
Symptoms	CBSQ. Significant		WSAS
Questionnaire	change in symptom		with direct effect of
(CBSQ)	attribution and		T → WSAS
Causal symptom	illness perceptions.		
attribution			
HADS			

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Table 2: Results Tables Continued

Study	Outcome Variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Jones et al (2011)	IBS Symptom Severity (BSSS)	RM- ANOVA	Anxiety (HADS) Depression (HADS)	Significant change in anxiety from baseline to midpoint but reversed from midpoint to end point.	Path analysis	Path model from T→SS with inclusion of different specified paths involving anxiety and depression.	Model not an adequate fit according to Chi ² goodness of fit (X ² =285.9, 29 df, P<.0005) Did not report findings for indirect paths.	N/A
Hunt et al (2009)	• IBS Symptom Severity (GSRS- IBS) • IBS- QoL	ANCOVA	Anxiety (ASI) GI specific anxiety (VAS) General catastrophizing (subscale CSQ) GI specific catastrophizing	Significant change in all outcome and mediating variables post treatment	ANCOVA utilising Baron & Kenny's framework	All mediator variables tested for indirect effects on symptom severity and IBS-QoL.	General catastrophizing found to mediate effect of treatment on symptom severity. No other mediation found.	N/A

(subscale CSQ)

Lackner et al (2007)	• IBS Symptom Severity (Visual Analogue Scale)	Two way ANOVA	Psychological distress (BSI) IBS QoLa	Psychological distress reduced (significance not reported) IBS QoL increased (significance not reported)	Path Analysis	Path model from T→SS, QoL, distress, with bidirectional paths between all three variables to each other.	Model fit not reported.	Model fit not reported
	• IBS QoL						No significant mediation effect on symptom severity reported	T→SS → IBS QoL

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Table 2: Results Tables Continued

Study	Outcome Variable/s	Main effect analysis	Mediator variables	Effect of intervention on mediators	Mediation analysis	Indirect effects tested	Results: Mediating effects on symptom severity (SS)	Results: Mediating effects on QoL
Ljotsson et al (2013)	IBS Symptom Severity (GSRS-IBS)	Parallel process latent growth curve model	Gastrointestinal symptom specific anxiety (VSI) Stress (PSS)	Significant differences in linear growth rate of VSI Stress significantly decreased over time – no difference between groups	Parallel process latent growth curve model	Two separate parallel bivariate growth models conducted: T → VSI → GSRS-IBS T → PSS → GSRS-IBS	VSI found to significantly mediate the effect of treatment on GSRS. PSS did not significantly mediate the effect of treatment on GSRS	N/A
Wolitzky et al	IBS symptom	Hierarchical linear	Gastrointestinal symptom specific	Significantly reduced GSA.	Hierarchical Linear	Group x VSI slope interaction	VSI mediated treatment effect on outcome but not differentially	N/A

(2012)	severity (a	model	anxiety (VSI)	Model	across treatment and control groups.
	composite				
	bowel				
	symptom				
	severity				
	index,				
	BSSS)				
	• IBS-QoL				

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Table 3: Treatment models and intervention protocols used.

Study	Treatment Model Explicitly Referenced	Intervention Protocol Components
Garland et al (2008)	Mindfulness Based Stress Reduction tailored to IBS symptoms (Gaylord et al., 2009)	(1) Sitting, walking, yoga and body scan mediations. (2) Mindfulness tailored towards IBS by emphasizing relevance of mindfulness in coping with IBS-related symptoms and perceptions. (3) Psychoeducation component was included regarding the physiological relationship between stress and symptoms (4) Promotion of awareness of sensory versus emotional processing of interoceptive signals, with view to counteract catastrophizing.
Reme et al (2011)	CBT Three systems model (Kennedy et al., 2006a)	(1) Assessment of main symptom, precipitating factors, maintaining cognitions & behaviours, discussion of treatment rationale (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) Long term & short term behavioural goal setting with relation to symptoms- graded exposure (4) Behavioural experiments to test beliefs about consequences of IBS (5) Psychoeducation about stress and bowel symptoms (6) Problem solving and symptom & stress management techniques (7) Managing flare ups
Labus et al (2012)	Biopsychosocial model of IBS	(1) Psychoeducation about stress, IBS self management regarding diet and medication (2) Psychoeducation regarding role of symptom appraisal, beliefs and attitudes and links between cognitions, mood, stress, behavioural responses and symptoms (3) Alternative responses (4) Relaxation exercises (5) Monitoring symptoms, behaviours & cognitions and interrelations

Chilcot & Moss-Morris (2013)	CBT (Moss-Morris et al., 2010)	Treatment rationale explained (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) General consideration of unhelpful cognitions, perfectionism and patterns of boom/bust (4) Long term & short term behavioural goal setting with relation to symptoms-graduated exposure (5) Psychoeducation about stress and bowel symptoms, sleep hygiene (6) Problem solving and symptom & stress management techniques including relaxation techniques (7) Managing flare ups
Jones et al (2011)	CBT/Biopsychosocial model (Jones et al., 2011)	(1) Realistic symptom appraisal (2) Enhanced coping strategies (3) Cognitive restructuring (4) Problem solving
Hunt et al (2009)	CBT with inclusion of module targeting IBS specific catastrophizing (Hunt et al., 2009)	(1) Psychoeducation about stress and bowel symptoms (2) Relaxation training (3) Monitoring cognitions & emotions (4) IBS specific catastrophizing, thought records & identification of interrelationship between IBS-specific cognitions, behaviours, emotions and symptoms (5) Graduated exposure (6) Behavioural experiments to test beliefs about social consequences of IBS

Lackner et al (2007)	CBT (Blanchard et al., 2007)	(1) Psychoeducation about stress and bowel symptoms (2) Monitoring symptoms, behaviours & cognitions and interrelations (3) Problem solving and symptom & stress management techniques (4) Relaxation training (5) cognitive restructuring for modifying faulty threat appraisals that underlie physiologic and emotional reactivity
Ljotsson et al (2013)	Exposure Based Cognitive Behavioural Therapy (Ljótsson et al., 2011)	(1) Mindfulness exercises to promote awareness of interrelationship between GI symptoms, cognitions, emotions, behaviours/behavioural impulses (2) Exposure exercises & behavioural experiments
Wolitzky et al (2012)	Adapted protocol of CBT for panic disorder (DeCola, 2001, Craske and Barlow, 2006)	(1) Cognitive restructuring of IBS specific beliefs (2) Exposure exercises & behavioural experiments (3) Attentional control skills to reduce symptom focussing

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